ORIGINAL ARTICLE

CLINICAL GASTROENTEROLOGY

doi.org/10.1590/S0004-2803.24612023-131

Influence of neoadjuvant therapy on the ratio of lymph nodes

Laura **CREDIDIO**, Carlos Augusto Real **MARTINEZ**, Daniéla Oliveira **MAGRO**, Rita Barbosa de **CARVALHO**, Maria de Lourdes Setsuko **AYRIZONO** and Cláudio Saddy Rodrigues **COY***

*Universidade Estadual de Campinas, Grupo de Coloproctologia da Disciplina de Doenças do Aparelho Digestivo, Campinas, SP, Brasil.

HIGHLIGHTS

- Assessment of the lymph nodes during pathological analysis of the surgical specimen is crucial to determine treatment and prognosis.
- Neoadjuvance therapy reduces the number of lymph nodes, being lower than recommended, therefore the lymph node ratio can be an alternative analysis for a better prognosis.

ABSTRACT – Background – To evaluate the relationship between the ratio of affected lymph nodes (LNR) and clinical and anatomopathological variables in patients with rectal adenocarcinoma submitted or not to neoadjuvant chemoradiotherapy. **Methods –** The LNR was determined by dividing the number of compromised LNR by the total number of LNR dissected in the surgical specimen. Patients were divided into two groups: with QRT and without QRT. In each group, the relationship between LNR and the following variables was evaluated: degree of cell differentiation, depth of invasion in the rectal wall, angiolymphatic /perineural invasion, degree of tumor regression and occurrence of metastases. The LNR was evaluated in patients with more than 1, LNR (LNR >12) or less (LNR<12) in the surgical specimen with overall survival (OS) and disease-free survival (DFS). The results were expressed as the mean with the respective standard deviation. Qualitative variables were analyzed using Fisher's exact test, while quantitative variables were analyzed using the Kruskal -Wallis and Mann-Whitney tests. The significance level was 5%. **Results –** We evaluated 282 patients with QRT and 114 without QRT, between 1995–2011. In the QRT Group, LNR showed a significant association with mucinous tumors (P=0.007) and degree of tumor regression (P=0.003). In both groups, LNR was associated with poorly differentiated tumors (P=0.001, P=0.02), presence of angiolymphatic invasion (P<0.0001 and P=0.01), perineural (P=0.0007, P=0.02), degree of rectal wall invasion (T3>T2; P<0.0001, P=0.02); Compromised LNR (P<0.0001, P<0.01), metastases (P<0.0001, P<0.01). In patients with QRT, LNR<12 was associated with DFS (5.889; 95%CI1.935–19.687; P=0.018) and LNR>12 with DFS and OS (17.984; 95%CI5.931–54.351; P<0.001 and 10.286; 95%CI 2.654–39.854; P=0.007, respectively). **Conclusion –** LNR was associated with histological aspects of poor prognosis, regardless of the use of QRT. In the occurrence of less than 12 evaluated LNR, the LNR was associated only with the DFS.

Keywords – Ratio of lymph nodes; neoadjuvant therapy; colorectal cancer.

Received: 11 September 2023
Accepted: 22 November 2023

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
Declaration of use of artificial intelligence: none
Corresponding author: Laura Credidio. E-mail: laurabio@gmail.com

INTRODUCTION

The standard treatment for advanced extraperitoneal adenocarcinoma of the rectum is the use of neoadjuvant therapy followed by surgery. It is known that one of the main prognostic factors of this condition is associated with lymph node involvement. Different aspects associated with metastases in lymph nodes (LNR) have been related to prognostic factors such as extracapsular invasion and number of affected LNR. Several studies[1,2] demonstrate the importance of the ratio between the number of affected and resected LNR as a prognostic factor. It is now known that the use of neoadjuvant therapy decreases the number of LNR in surgical specimens[3-5] ,which may prevent adequate postoperative staging. Thus, it is speculated whether the ratio between the number of affected and examined LNR could be associated with prognostic factors, even in cases with less than 12 LNR in surgical specimens.

There is an increase in the number of early invasive colorectal cancers being diagnosed[6]. Currently, for colorectal cancer (CC) staging, the TNM classification is used, which analyzes, from the primary tumor (T), the depth of invasion, number of affected LNR (N) and distant metastasis (M)[7,8], with the presence of LNR in the surgical specimen being an important factor in the prognosis and treatment of CC[7-11]. Chou et al. demonstrated that only 49% of patients with colorectal cancer undergoing surgery had the minimum recommended number of LNR [12]. The American Joint Committee on Cancer recommends the resection of at least 12 LNR in the surgical specimen, however, this number depends on an adequate surgical resection and a good pathologist, in addition to these variables, this number is significantly reduced in patients with colon rectal cancer, with less than 12 LNR usually being found in the surgical specimen[3,4,13-16]. In studies on the size of the resection and the proportion of LNR influencing colorectal cancer, it was observed that the increase in the size of the resection causes an increase in the proportion of LNR, however, without affecting the number of positive LNR, thus constituting a factor that alters the conclusion of the prognostic value of the proportion of LNR[17-19]. Added to this, the prognostic importance of the number of LNR, in patients with few resected LNR, compared with patients with many resected LNR, after QRT, is not completely elucidated[20]. For this reason, the ratio of affected LNR (total number of LNR/N of affected LNR) is being considered an important prognostic factor in CC, and may be an alternative with better prognostic accuracy. The importance of LNR status as a confirmed prognostic factor for patient survival is also highlighted. In one study, a 5-year survival occurred in 63.9% of 144 patients analyzed[21].

Although almost all studies have shown LNR as an independent risk factor, its superiority over the TNM system is not generally accepted[22], this is because there is no agreement on the best cut-off points for using the LNR. Furthermore, contradictory results of LNR have been reported in patients with inadequate LNR dissection[23,24]. There are still no data showing the prognostic value of LNR in patients with rectal cancer undergoing neoadjuvant therapy.

The objective is to evaluate the relationship between LNR with clinical and anatomopathological variables, disease-free survival (DFS) and overall survival (OS) in patients with CC submitted or not to QRT.

METHODS

Retrospective longitudinal study with patients with sporadic CC operated on at the *Hospital de Clínicas da* UNICAMP by the Coloproctology Group, FCM, UNICAMP. Reference in the treatment of colorectal cancer in Brazil with a team formed by four chiefs following the same protocol in all surgeries assisted by residents. Epidemiological aspects (sex, race), histological diagnosis and whether or not of neoadjuvant therapy. Patients who underwent neoadjuvant treatment were those where the tumor was in the extraperitoneal segments of the rectum. Patients who did not undergo this treatment have rectal neoplasms, but above the peritoneal reflection.

The TNM classification[15] was used and the following histological characteristics were considered: type (usual adenocarcinoma or mucinous adenocarcinoma); cell differentiation (well, poorly and moderately differentiated); vascular, angiolymphatic and perineural invasion; compromised margins, tumor invasion, number of LNR in the surgical specimen, number of LNR with (N+) and without neoplastic in-

volvement (N-) and ratio of affected LNR. The lymph node ratio was calculated by dividing the total number N+ by the total number of LNR found in the surgical specimen. Patients were divided into two groups: with QRT (+QRT) or without QRT (-QRT). In the +QRT group, cases with N- were stratified by the total number of LNR, less than 12 and greater than or equal to 12.

Disease-free time was defined as the period between surgery with total macroscopic resection (R0) and the appearance of metastasis or local recurrence and OS was assessed through telephone contact, the patient's last appointment or death report.

Inclusion criteria were patients diagnosed with rectal adenocarcinoma. Patients with Familial Adenomatous Polyposis, Lynch syndrome or inflammatory bowel disease were excluded.

This project was approved by the local Ethical Committee under number 2.294.165 and was carried out in accordance with Resolution 466/2012.

Diagnosis and treatments

It is known that the complete resection of the primary tumor in cases of colorectal cancer with removal of the LNR in the region is also one of the most important conducts of the treatment[7].

In this study, all patients underwent rectal physical examination and colonoscopy with biopsy to confirm colorectal cancer, 282 with neoadjuvant treatment (+QRT), 114 with no neoadjuvant treatment (-QRT) and 14 patients without treatment information. Those with neoadjuvant treatment or adjuvant treatment followed the oncological protocol in all patients.

Pathological analyzes

After surgery, the samples were fixed with formalin solution, is performed between 3 to 5 days after the surgical procedure being by the same pathologist with more than 20 years of experience and the LNs were dissected using manual palpation. The pathological stage of the tumor was determined according to the AJCC staging system (7th edition)[15,25] and marked as ypTNM , when the patient underwent preoperative QRT and pTNM if not. Tumors were evaluated for histological type, N stage, T stage, tumor differentiation, vascular and lymphatic invasion, perineural invasion and pathological response. The number of LNs examined, the number of positive LNs determined, the lymphatic vascular invasion and the LNR were calculated for each patient.

Statistical analysis

For statistical analysis, the following computer programs were used: The SAS System for Windows (Statistical Analysis System), version 9.4. SAS Institute Inc, 2002–2008, Cary, NC, USA. Descriptive statistics were reported for relevant variables. To assess survival and disease-free time, Cox regression analysis was used. To assess the relationship between QRT and tumor staging, Fisher's exact test was used.

To study the relationship between the ratio of compromised LNR and the histological characteristics, the Kruskal-Wallis and Mann - Whitney tests were used. When necessary to identify the difference found in the Kruskal-Wallis test, Dunn's post-hoc test was used. To establish the cutoff points, ROC curves were constructed for the lymph node ratio.

The significance level adopted for this study was 5%.

RESULTS

A total of 410 patients were analyzed, with a mean age of 60.87 years (29–87), 54.63% male and 84.07% Caucasian (TABLE 1). The mean OS was 4.76 years and DFS 4.02 years.

Neoadjuvant therapy was used in 71.2%, and of these there was no evidence of tumor regression at histological examination in 51.64%.

In the analysis of histological characteristics, 85.79% were classified as moderately differentiated, and absence of angiolymphatic and perineural invasion in 68.11% and 81.03%, respectively. As for tumor invasion, 58.78% were classified as T3 and 92.71% had tumor-free surgical margins. In 61.95% of the cases there was no involvement of LNR and no metastases in 86.83%.

The mean number of LNR was 20.2 LNR and the mean number of N+ was 5.37. In 33.41% of the cases, less than 12 LNR were identified in the surgical specimen, and of these, 84.67% underwent neoadjuvant treatment. In six cases no LNR were identified in the specimen, five in patients with neoadjuvant therapy. The mean LNR was 0.109 (0–0.8; +0.21). In the –

TABLE 1. Epidemiological aspects.

Gender	
Female	45.37%
Male	54.63%
Race	
White	84.10%
Black	4.90%
Brown	9.80%
Asian	1.23%
Neodjuvant treatment	
Yes	71.21%
No	28.79%
Survive	
Yes	71.95%
No	28.05%
Metastasis	
Yes	37.56%
No	62.44%
Histology	
Adenocarcinoma	78.05%
Mucinous Carcinoma	13.66%
Others	8.29%
Complete response for neoadjuvant	
Yes	8.66%
No	91.34%
Lymph node staging	
N0	61.95%%
N1	20.98%%
N2	17.07%

QRT group, the number of total LNR, compromised LNR and LNR was significantly higher, *P*=0.00072; *P*=0.00187; *P*=0.0186, respectively.

In the +QRT group, the LNR showed a significant difference in relation to histological type (*P*=0.0071), degree of tumor differentiation (*P*=0.0017), pT3 vs pT2, presence of angiolymphatic (*P*<0.0001) and perineural (*P*=0.0007) invasion, histological response and presence of metastasis. The LNR was lower in surgical specimens with complete response (*P*=0.0033).

In the -QRT group, the LNR showed significance regarding tumor differentiation, pT3 vs pT2 stage, angiolymphatic and perineural invasion and presence of metastasis.

Compromised margins correlated with a higher rate of LNR in patients without neoadjuvant therapy (*P*=0.0041).

Among N0 patients in the +QRT group, there were no differences regarding OS and DFS when surgical specimens with more and less than 12 lymph nodes were compared (TABLE 2).

TABLE 2. Evaluation of DFS and OS for LNR; N (cox regression).

		No	RR	CI95%	*P*
DFS					
no x yes			1.193	0.735–1.935	0.4747
OS					
no x yes			1.545	0.863–2.766	0.1428
+QRT and N=0					
DFS		182			
>12x<12			1.117	0.629–1.985	0.7058
OS		182			
>12x<12			0.867	0.464–1.617	0.6528
+ QRT <12 lymph					
DFS		108	**5.889**	1935–19687	**0.0018**
	N1 x N0		**5.193**	2630–10253	**<0.0001**
	N2 x N0		2.543	0.750–8.620	
OS		108	1825	0.367–9.083	0.4623
	N1 x N0		**2.639**	1.132–6.149	**0.0470**
	N2 x N0		2.532	0.743–8.626	
+ QRT >12 lymph					
DFS		174	**17.984**	5.931–54.531	**<0.0001**
	N1 x N0		1.460	0.785–2.715	
	N2 x N0		**4.270**	2.386–7.644	**<0.0001**
OS		174	**10.286**	2.654–39.854	**0.0007**
	N1 x N0		**1.573**	0.779–3.179	**0.0020**
	N2 x N0				
- QRT >12 lymph node					
DFS		93	**9.775**	**3.541–26.985**	**<0.0001**
	N1 x N0		**3.232**	**1.364–7.658**	**0.0001**
	N2 x N0		**5.018**	**2.367–10.639**	
OS		93	**31.256**	**8.762–111.490**	**<0.0001**
	N1 x N0		1942	0.563–6.699	**0.0032**
	N2 x N0		**4.829**	**1901–12267**	

+QRT: with preoperative chemoradiotherapy treatment; -QRT: no preoperative chemoradiotherapy treatment; DFS: disease-free survival; OS: overall survival; LNR: lymph nodes.

Among patients with LNR >10%, no statistical difference was observed in relation to OS and DFS in the groups with and without QRT (TABLE 3).

The Roc curves did not show a cut-off value for the2 LNR in relation to DFS (FIGURE 1), OS (FIGURE 2) and angiolymphatic invasion.

TABLE 3. Evaluation of survival and disease-free time for LNR without neoadjuvant therapy.

	No	RR	CI95%	*P*
+QRT x LNR				
DFS	282			
		9.278	**4.373–19.687**	**<0.0001**
OS	282			
		4.241	**1566–11483**	**0.0045**
-QRT x LNR				
DFS	114			
		8.674	**3.655–20.584**	**<0.0001**
OS	114			
		13.157	**4.675–37.024**	**<0.0001**
+QRT: >12x<12				
DFS	282			
		0.985	0.659–1.472	0.9422
OS	282			
		0.931	0.585–1.483	0.7641
-QRT: >12x<12				
DFS	114			
		1.160	0.519–2.580	0.7177
OS	114			
		0.614	0.276–1.363	0.2308
+QRT x -QRT				
DFS	410			
		1.288	0.914–1.816	0.3172
OS	396			
		1.178	0.941–4.428	0.1731

+QRT: with preoperative chemoradiotherapy treatment; -QRT: no preoperative chemoradiotherapy treatment; LNR: lymph nodes.

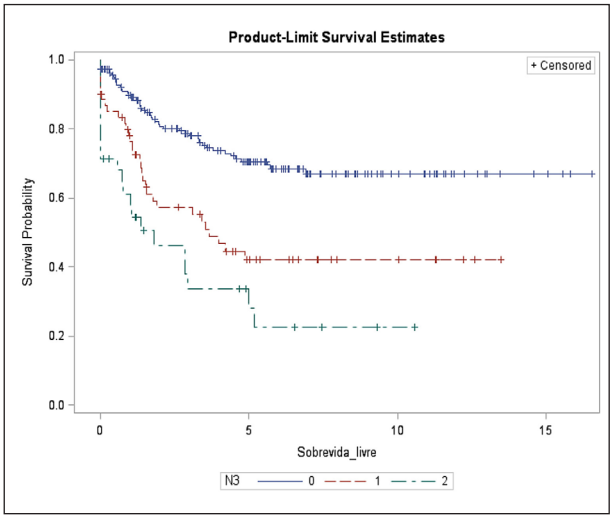

FIGURE 1. DFS with QRT.

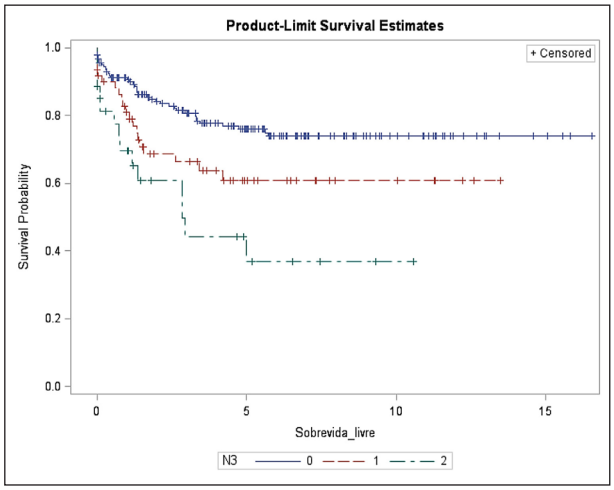

FIGURE 2. OS with QRT.

The Kaplan Meier curve showed no difference in the disease-free time regarding the number of N0 LNR in the specimens (greater than 12 and less than 12) in the +QRT groups.

DISCUSSION

This study investigated the predictive ability of LNR in CC. Several studies have shown that LNR is a promising prognostic value, independent of UICC/AJCC TNM, in patients with neoadjuvant treatment, as LNR involvement is considered one of the most important prognostic factors in cancer treatment and adjuvant therapy[1,2,13,26].

There is no consensus in the literature on the minimum number of LNR needed to accurately identify early-stage rectal cancer[27]. Most of these studies combined rectal and colon cancers with surgery as the initial treatment. Two studies with CC alone reported 14 and >10 LNR as the minimum number to accurately identify stage II rectal cancer[28,29], however, studies show that QRT reduces the number of local LNR[20]. Furthermore, the mean number of LNR recovered from rectal cancers treated with neoadjuvant therapy is significantly lower than those treated by surgery alone (13 vs 19, $P<0.05$; 7 vs 10, $P\leq0.001$)[3,4,15,30]. Our findings corroborate data from the literature. In our study the mean number of lymph nodes in patients with QRT was 19.94 while in patients without QRT it was 26.35, significantly lower ($P<0.05$). The same occurred with the number of compromised LNR found in the surgical specimens.

Habr Gama et al.[31] reported that 11% of the resected specimens had complete absence of LNR, 32 of 281 irradiated patients had favorable pathological characteristics in relation to tumor (T) and perineural invasion, diverging with our data, which were similar to the findings by Raoof et al.[32], where 2.37% of the patients did not present any LNR in the surgical specimen, 7 of 295 irradiated patients.

With all these divergences about the LNR, an alternative to the pN staging emerged, the LNR, for having a greater statistical power for the analysis of survival and being corroborated by several authors[13,26,33,34]. However, the best way is still being discussed, many authors defend the division by quartiles, but studies are controversial, Bhatti et al.[35] did not find, in the quartiles, a significant variable for survival. A meta-analysis was performed in 2017 by Chengwu Jin et al.[2] reporting that there are still doubts about the cutoff value. Our findings also did not identify a cutoff point in relation to OS, DFS and angiolymphatic invasion in relation to LNR, in order to try to find the cutoff point, we excluded specimens without lymph node involvement (N-), with this we obtained a reduced number of samples, this may have influenced the result.

We could observe that the higher the LNR, the greater the risk of death and metastasis, in both groups. In the –QRT group, the risk of death is 3 times greater when compared to the +QRT group, data corroborated in a recent study carried out by Lee et al.[36] where the high LNR index resulted in worse OS and DFS in colon and rectum cancer. These findings corroborate the meta-analysis carried out by Chengwu Jin et al.[2], the study concludes that a high LNR index predicts a low survival rate in advanced rectal cancer. The comparison of the LNR between surgical specimens with less than 12 and more than 12 lymph nodes, regarding OS and DFS, was not significant (P=0.4824), these results were similar to Nadoshan et al.[10].

Several studies report that stage III also showed a worse OS and DFS[11,13,36], our study, regarding staging, there was no significance in both groups, however we obtained a significant result, patients with neoadjuvant therapy and complete response to treatment, presented the lowest LNR when compared to usual and mucinous adenocarcinoma (P=0.0071).

We carried out an analysis based on the LNR regarding the pN and we were able to verify that, in both groups, with and without QRT, the increase in the LNR decreases the DFS and OS in patients with pN + in relation to patients with pN -, however the patients –QRT the risk of death was 7 times greater than +QRT. Some similar findings were reported by Lee et al.[26] where they performed a survival analysis based on the LNR in ypN 1 and ypN 2, finding that the 5-year OS and DFS rates tend to decrease with the increase in the LNR, although these differences were not statistically significant due to the low power resulting from the small number of patients included in each subgroup, they also found that the 5-year OS and DFS rates for patients with ypN1 and LNR >0.3 were similar or worse than those for patients with ypN2. In our study, we evaluated with and without QRT and LNR >10%, in both cases there was no significant difference in relation to OS and DFS. Our results were also similar to Bhatti et al.[35] in which patients with ypN1 or ypN2 had similar survival.

When we compared the OS and DFS in patients with <12 and >12 LNR in the surgical specimen, with ypN - there was no statistical significance (P=0.867 and P=1.117), findings similar to those of Bhatti et al.[35] McFadden et al.[37], Rullier et al.[38], Ha et al.[39], Klos et al.[40] and La Torre et al.[41], but diverging from findings by Mekenkamp et al.[42] where patients with <7 LNR had lower DFS when compared to patients with >8 LNR, this may have occurred due to the cut-off number of LNR that differed from those mentioned above . However, regarding the analysis of the RR of patients +QRT <12 and > 12 LNR in relation to LNR, the increase in LNR increases the risk of recurrence by 3 x and of death by 5.6 x more in patients with ≥12 LNR in relation to patients with <12 LNR, findings similar to Lee et al.[10] evaluated the prognostic effect of LNR in 154 cases of rectal cancer and found the prognostic impact of LNR on DFS and OS of patients with less than 12 LNR and more than 12 total LNR in the surgical specimen. Bhatti et al.[35] observed a high percentage of patients with ypN1 and <12 LNR (22.4%) and ypN2 in >12 LNR (29.8%), but the distribution was not significant. In our study the percentages were similar, and also not significant, ypN1 in patients with <12 LNR (21.6%) and ypN2 in

>12 LNR (28.4%), however our percentage in ypN2 with <12 LNR was well lower than the study mentioned above (21.4% versus 9.8%).

A significant finding that we did not find reference in the literature, was in relation to surgical margins free of tumor in the surgical specimen in relation to LNR. In patients with neoadjuvant therapy, LNR was similar between specimens with margins compromised by the tumor and tumor-free margins, however, in patients without neoadjuvant therapy, there was an increase in LNR, with statistical significance, showing that QRT protects against the involvement of lymph nodes in cases of compromised margins.

Our study demonstrated that the increase in LNR presents a worse prognosis of the disease, lower DFS and lower OS, and can be used mainly in the prognosis of patients with <12 LNR of the surgical specimens. However, we agree that several factors influence the LNR findings, anatomical and physiological factors of the patients, extent and technique of surgical dissection and an adequate pathological analysis and the neoadjuvant treatment itself.

Some limitations were found, such as loss of follow-up and lack of death certificate, which is why it was considered the patient's last service recorded in the medical record or telephone contact, for those who attended.

CONCLUSION

QRT decreases the LNR, having a protective effect on the involvement of LNR in cases of compromised margins; LNR was associated with histological aspects of poor prognosis, regardless of the use of QRT.

In the occurrence of less than 12 LNR evaluated, the LNR correlated with the DFS, and with the OS.

In patients with CC, every 10% increase in LNR was associated with a higher risk of death in patients without QRT, but not with DFS.

Authors' contribution

Credidio L: contributed to the preparation of the project, wrote the article and collected data. Martinez CAR: contributed to the preparation of the project, statistical analysis. Magro DO: critical review and statistical analysis. Carvalho RB: pathological analysis of surgical specimens. Ayrizono MLS: contributed to the preparation of the project. Coy CSR: coordinated the project from start to review.

Orcid

Laura Credidio: 0000-0003-0929-7800.
Carlos A Real Martinez: 0000-0001-8088-427X.
Daniéla Oliveira Magro: 0000-0002-8180-6254.
Rita Barbosa de Carvalho: 0000-0002-4367-9311.
Maria de Lourdes S Ayrizono: 0000-0002-7035-2568.
Cláudio S Rodrigues Coy: 0000-0002-0916-4138.

Credidio L, Martinez CAR, Magro DO, Carvalho RB, Ayrizono MLS, Coy CSR. Influência da terapia neoadjuvante na razão de linfonodos. Arq gastroenterol. 2024;61:e2?.

RESUMO – Contexto – Avaliar a relação entre a razão de linfonodos (RLA) acometidos e variáveis clínicas e anatomopatológicas em portadores de adenocarcinoma de reto submetidos ou não à quimiorradioterapia neoadjuvante. **Métodos –** A RLA foi determinada dividindo-se o número total de linfonodos (LFNs) dissecados no espécime cirúrgico pelo número de comprometidos. Os doentes foram divididos em dois grupos: com QRT e sem QRT. Em cada grupo foi avaliada a relação entre a RLA e as seguintes variáveis: grau de diferenciação celular, profundidade de invasão na parede retal, invasão angiolinfática/perineural, grau de regressão tumoral e ocorrência de metástases. Avaliou-se a RLA em pacientes com mais do que 12 LFNs (RLA>12) ou menos (RLA<12) na peça cirúrgica com a sobrevida global (SG) e sobrevida livre de doença (SLD). Os resultados foram expressos pela média com o respectivo desvio padrão. As variáveis qualitativas foram analisadas utilizando-se o teste exato de Fisher, enquanto as quantitativas pelos testes de Kruskal-Wallis e Mann-Whitney. O nível de significância foi de 5%. **Resultados –** Foram avaliados 282 pacientes com QRT e 114 sem QRT, entre 1995–2011. No Grupo QRT, RLA mostrou associação significativa com os tumores mucinosos (P=0,007) e grau de regressão tumoral (P=0,003). Nos dois grupos, a RLA associou-se com tumores pouco diferenciados (P=0,001 e P=0,02), presença de invasão angiolinfática (P<0,0001 e P=0,01), perineural (P=0,0007 e P=0,02), grau de invasão da parede retal (T3>T2; P<0,0001 e P=0,02); LFNs comprometidos (P<0,0001 e P<0,01), metástases (P<0,0001 e P<0,01). Nos pacientes com QRT, a RLA <12 associou-se com a SLD (5,889; IC95%1,935–19,687; P=0,018) e a RLA >12 com SLD e SG (17,984; IC95%5,931–54,351; P<0,001 e 10,286; IC95%2,654–39,854; P=0,007, respectivamente). **Conclusão –** A RLA associou-se a aspectos histológicos de mau prognóstico, independentemente do emprego de QRT. Na ocorrência de menos de 12 LFNs avaliados, a RLA associou-se apenas com a SLD.

Palavras-chave – Razão de linfonodos; terapia neadjuvante; câncer colorretal.

REFERENCES

1. Priolli DG, Cardinalli IA, Pereira JA, Alfredo CH, Margarido NF, Martinez CAR. Metastatic lymph node ratio as an independent prognostic variable in colorectal cancer: study of 113 patients. Tech Coloproctol. 2009;13:113.
2. Jin C, Deng X, Li Y, He W, Yang X, Liu J. Lymph node ratio is an independent prognostic factor for rectal cancer after neoadjuvant therapy: A meta-analysis. J Evid Based Med. 2018;11:169-75. doi: 10.1111/jebm.12289.
3. Wichmann MW, Müller C, Meyer G, Strauss T, Hornung HM, Lau-Werner U, et al. Effect of preoperative radiochemotherapy on lymph node retrieval after resection of rectal cancer. Arch Surg. 2002;137:206-10.
4. Baxter NN, Morris AM, Rothenberger DA, Tepper JE. Impact of preoperative radiation for rectal cancer on subsequent lymph node evaluation: A population-based analysis. Int J Radiat Oncol. 2005;61:426-31.
5. De La Fuente SG, Manson RJ, Ludwig KA, Mantyh CR. Neoadjuvant Chemoradiation for Rectal Cancer Reduces Lymph Node Harvest in Proctectomy Specimens. J Gastrointest Surg. 2009;13:269-74.
6. Dang H, van Pelt GW, Haasnoot KJC, Backes Y, Elias SG, Seerden TCJ, et al. Tumour-stroma ratio has poor prognostic value in nonpedunculated T1 colorectal cancer: A multicentre case-cohort study. United Eur Gastroenterol J. 2021;9:478-85.
7. Kim HJ, Choi GS. Clinical Implications of Lymph Node Metastasis in Colorectal Cancer: Current Status and Future Perspectives. Ann Coloproctology. 2019;35:109-17.
8. Macedo F, Sequeira H, Ladeira K, Bonito N, Viana C, Martins S. Metastatic lymph node ratio as a better prognostic tool than the TNM system in colorectal cancer. Future Oncol. 2021;17:1519-32.
9. Andrade VA, Coy CS, Leal RF, Fagundes JJ, Martinez CA, Ayrizono Mde L. Neoadjuvant Therapy and Surgery for Rectal Cancer. Comparative study between partial and complete pathological response. Arq Gastroenterol. 2016;53:163-8.
10. Nadoshan JJ, Omranipour R, Beiki O, Zendedel K, Alibakhshi A, Mahmoodzadeh H. Prognostic value of lymph node ratios in node positive rectal cancer treated with preoperative chemoradiation. Asian Pac J Cancer Prev. 2013;14:3769-72.
11. Lykke J, Jess P, Roikjaer O. The prognostic value of lymph node ratio in a national cohort of rectal cancer patients. Eur J Surg Oncol EJSO. 2016;42:504-12.
12. Chou JF, Row D, Gonen M, Liu YH, Schrag D, Weiser MR. Clinical and pathologic factors that predict lymph node yield from surgical specimens in colorectal cancer. Cancer. 2010;116:2560-70.
13. Leonard D, Remue C, Abbes Orabi N, van Maanen A, Danse E, Dragean A, et al. Lymph node ratio and surgical quality are strong prognostic factors of rectal cancer: results from a single referral centre. Colorectal Dis. 2016;18:O175-84.
14. Chang KH, Kelly NP, Duff GP, Condon ET, Waldron D, Coffey JC. Neoadjuvant therapy does not affect lymph node ratio in rectal cancer. The Surgeon. 2016;14:270-3.
15. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010. p.646.
16. Khare S, Verma M. Epigenetics of colon cancer. Methods Mol Biol Clifton NJ. 2012;863:177-85.
17. Zanghì A, Cavallaro A, Lo Menzo E, Curella Botta S, Lo Bianco S, Di Vita M, et al. Is there a relationship between length of resection and lymph-node ratio in colorectal cancer? Gastroenterol Rep. 2020;9:234-40.
18. Mei SW, Liu Z, Wang Z, Pei W, Wei FZ, Chen JN, et al. Impact factors of lymph node retrieval on survival in locally advanced rectal cancer with neoadjuvant therapy. World J Clin Cases. 2020;8:6229-42.
19. Barrio I, Roca-Pardiñas J, Arostegui I. Selecting the number of categories of the lymph node ratio in cancer research: A bootstrap-based hypothesis test. Stat Methods Med Res. 2021;30:926-40.
20. Mechera R, Schuster T, Rosenberg R, Speich B. Lymph node yield after rectal resection in patients treated with neoadjuvant radiation for rectal cancer: A systematic review and meta-analysis. Eur J Cancer. 2017;72:84-94.
21. Benedek Z, Boer ST, Bauer O, Sardi K, Todor A, Suciu N, et al. An Overview of Five-Year Survival in Rectal Cancer in Relation to Lymph Node Status. Chirurgia (Bucur). 2020;115:747.
22. McMillan DC, McArdle CS, Morrison DS. A clinical risk score to predict 3-, 5- and 10-year survival in patients undergoing surgery for Dukes B colorectal cancer. Br J Cancer. 2010;103:970-4.
23. Song YX, Wang ZN, Xu YY, Tong LL, Zhu JL, et al. Integrated Ratio of Metastatic to Examined Lymph Nodes and Number of Metastatic Lymph Nodes into the AJCC Staging System for Colon Cancer. PLoS One. 2012;7:e35021.
24. Le Voyer TE, Sigurdson ER, Hanlon AL, Mayer RJ, Macdonald JS, Catalano PJ, et al. Colon Cancer Survival Is Associated With Increasing Number of Lymph Nodes Analyzed: A Secondary Survey of Intergroup Trial INT-0089. J Clin Oncol. 2003;21:2912-9.
25. Pei JP, Zhang R, Zhang NN, Zeng YJ, Sun Z, Ma SP, et al. Screening and validation of a novel T stage-lymph node ratio classification for operable colon cancer. Ann Transl Med. 2021;9:1513.
26. Lee SD, Kim TH, Kim DY, Baek JY, Kim SY, Chang HJ, et al. Lymph node ratio is an independent prognostic factor in patients with rectal cancer treated with preoperative chemoradiotherapy and curative resection. Eur J Surg Oncol EJSO. 2012;38:478-83.
27. Wong SL, Ji H, Hollenbeck BK, Morris AM, Baser O, Birkmeyer JD. Hospital lymph node examination rates and survival after resection for colon cancer. JAMA. 2007;298:2149-54.
28. Pocard M, Panis Y, Malassagne B, Nemeth J, Hautefeuille P, Valleur P. Assessing the effectiveness of mesorectal excision in rectal cancer: Prognostic value of the number of lymph nodes found in resected specimens. Dis Colon Rectum. [Internet]. 1998;41:839-45. Available from: https://journals.lww.com/dcrjournal/Fulltext/1998/41070/Assessing_the_effectiveness_of_mesorectal_excision.5.aspx
29. Tepper JE, O'Connell MJ, Niedzwiecki D, Hollis D, Compton C, Benson III AB, et al. Impact of Number of Nodes Retrieved on Outcome in Patients With Rectal Cancer. Jounal Clin Oncol. 2001;19:157-63.
30. Han J, Noh GT, Yeo SA, Cheong C, Cho MS, Hur H, et al. The number of retrieved lymph nodes needed for accurate staging differs based on the presence of preoperative chemoradiation for rectal cancer. Medicine (Baltimore). 2016;95:e4891.
31. Habr-Gama A, Perez RO, Proscurshim I, Rawet V, Pereira DD, Sousa AHS, et al. Absence of Lymph Nodes in the Resected Specimen After Radical Surgery for Distal Rectal Cancer and Neoadjuvant Chemoradiation Therapy: What does it Mean? Dis Colon Rectum. [Internet]. 2008;51:277-89. Available from: https://journals.lww.com/dcrjournal/Fulltext/2008/51030/Absence_of_Lymph_Nodes_in_the_Resected_Specimen.2.aspx
32. Raoof M, Nelson RA, Nfonsam VN, Warneke J, Krouse RS. Prognostic significance of lymph node yield in ypN0 rectal cancer. BJS. 2016;103:1731-7.
33. Rosenberg R, Friederichs J, Schuster T, Gertler R, Maak M, Becker K, et al. Prognosis of Patients With Colorectal Cancer Is Associated With Lymph Node Ratio: A Single-Center Analysis of 3026 Patients Over a 25-Year Time Period. Ann Surg. [Internet]. 2008;248:968-78. Available from: http://journals.lww.com/annalsofsurgery/Fulltext/2008/12000/Prognosis_of_Patients_With_Colorectal_Cancer_Is.9.aspx
34. Kim YS, Kim JH, Yoon SM, Choi EK, Ahn SD, Wook LS, et al. Lymph Node Ratio as a Prognostic Factor in Patients With Stage III Rectal Cancer Treated With Total Mesorectal Excision Followed by Chemoradiotherapy. Int J Radiat Oncol. 2009;74:796-802.
35. Bhatti ABH, Akbar A, Hafeez A, Syed AA, Khattak S, Jamshed A, et al. Impact of lymph node ratio and number on survival in patients with rectal adenocarcinoma after preoperative chemo radiation. Int J Surg. 2015;13(Suppl):65-70.
36. Lee CHA, Wilkins S, Oliva K, Staples MP, McMurrick PJ. Role of lymph node yield and lymph node ratio in predicting outcomes in non-metastatic colorectal cancer. BJS Open. 2018;3:95-105.
37. McFadden C, McKinley B, Greenwell B, Kuckolls K, Culumovic P, Schammel D, et al. Differential lymph node retrieval in rectal cancer: Associated factors and effect on survival. J Gastrointest Oncol. 2013;4:158-63.
38. Rullier A, Laurent C, Capdepont M, Vendrely V, Belleannée G, Bioulac-Sage P, et al. Lymph Nodes After Preoperative Chemoradiotherapy for Rectal Carcinoma: Number, Status, and Impact on Survival. Am J Surg Pathol. [Internet]. 2008;32:45-50. Available from: https://journals.lww.com/ajsp/Fulltext/2008/01000/Lymph_Nodes_After_Preoperative_Chemoradiotherapy.7.aspx
39. Ha YH, Jeong SY, Lim SB, Choi HS, Hong YS, Chang HJ, et al. Influence of Preoperative Chemoradiotherapy on the Number of Lymph Nodes Retrieved in Rectal Cancer. Ann Surg. [Internet]. 2010;252:336-40. Available from: https://journals.lww.com/annalsofsurgery/Fulltext/2010/08000/Influence_of_Preoperative_Chemoradiotherapy_on_the.19.aspx

40. Klos CL, Bordeianou LG, Sylla P, Chang Y, Berger DL. The Prognostic Value of Lymph Node Ratio After Neoadjuvant Chemoradiation and Rectal Cancer Surgery. Dis Colon Rectum. [Internet]. 2011;54:171-5. Available from: http://journals.lww.com/dcrjournal/Fulltext/2011/02000/The_Prognostic_Value_of_Lymph_Node_Ratio_After.8.aspx
41. La Torre M, Mazzuca F, Ferri M, Mari FS, Botticelli A, Pilozzi E, et al. The importance of lymph node retrieval and lymph node ratio following preoperative chemoradiation of rectal cancer. Colorectal Dis. 2013;15:e382-8.
42. Mekenkamp LJM, van Krieken JHJM, Marijnen CAM, van de Velde CJH, Nagtegaal ID, for the Pathology Review Committee and the Co-operative Clinical Investigators. Lymph Node Retrieval in Rectal Cancer is Dependent on Many Factors—the Role of the Tumor, the Patient, the Surgeon, the Radiotherapist, and the Pathologist. Am J Surg Pathol [Internet]. 2009;33:1547-53. Available from: https://journals.lww.com/ajsp/Fulltext/2009/10000/Lymph_Node_Retrieval_in_Rectal_Cancer_is_Dependent.14.aspx